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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,450	02/27/2004	Grzegorz Bulaj	2699-5613.1US	8779

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EXAMINER	
GEBREYESUS, KAGNEW H	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 03/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,450	BULAJ ET AL.	
	Examiner	Art Unit	
	Kagnew H Gebreyesus	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *11-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) *1, 2, 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group I in the reply filed on January 19, 2005 is acknowledged. Claims 1-10 (as it applies to SEQ ID NO: 1 only) are at issue. Claims 11-27 are withdrawn from consideration as being part of a non-elected group.

The traversal is on the ground(s) that:

1) Even though the inventions are directed to independent and distinct inventions, the groups are sufficiently few and would not impose a burden in searching and examining.

2) That restriction within a Markush group is improper.

However, though the various enzymes share an overall common utility as disulfide isomerases, given that this restriction is between different enzymes with different sequences they do not share structural features by virtue of their different sequences disclosed as being essential to that utility. Each group necessarily requires both patent and non-patent as well as literature search that is independent. Although the search for the different groups of disulfide isomerases may overlap the search is not necessarily co-extensive as the applicant suggested. Furthermore contrary to applicant's argument, the search of the different amino acid sequences in all the commercial, non-commercial databases as well as the extensive database maintained at the office imposes an undue burden. Therefor the requirement for restriction is made FINAL.

Claim Objections

Claims 1, 2 and 9 are objected to as they continue to be directed to non-elected subject matter.

Claim 1 is objected to, the term "protein disulfide isomerase protein" because the term protein appears to be redundant. Applicant can overcome this objection by amending the claim to read as protein disulfide isomerase or disulfide isomerase.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1(f) and 9 (f) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear whether the "fragment" refers to nucleic acid sequence or a protein sequence.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 6, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are rejected over the recitation "host cell comprising a cell containing..." is not clear.

6. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are rejected over the recitation "comprise one or more nucleic acid molecules". The metes and bound of the claim is not clear.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 3- 9 and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid of SEQ ID NO: 1 encoding the protein disulfide isomerase (PDI) of SEQ ID NO: 2, vectors, host cells and a method of making the polypeptide of SEQ ID NO: 2 using said host cells, does not reasonably provide enablement for a sequence that has 57% sequence identity to the polypeptide encoded by SEQ ID NO: 1 or to a fragment thereof with protein disulfide isomerase activity or vector and host cell comprising the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 1, 3-10 are so broad as to encompass polynucleotides encoding any PDI comprising polypeptide having 57% identity to SEQ ID NO: 2 and fragments thereof. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotide sequences encoding protein disulfide isomerases

broadly encompassed by the claims. Since the polynucleotide encoding the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence corresponding to changes in the nucleic acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence corresponding to which nucleotides in the DNA sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure encoded by the nucleic acid sequence relates to its function. However, in this case the disclosure is limited to the nucleotide sequence of SEQ ID NO: 1 encoding the polypeptide of SEQ ID NO: 2.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of polynucleotides encoding any PDI with 57% identity to the protein disulfide isomerase encoded by SEQ ID NO: 1 because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting protein disulfide isomerase activity; (B) the general tolerance of protein disulfide isomerase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying

any number of residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides encoding protein disulfide isomerase with an enormous number of possible modifications of the protein disulfide isomerase of SEQ ID NO: 2. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of protein disulfide isomerase genes having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 3-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamauchi et al. (1988) or by Toyoshima et al. (1988). Yamauchi et al., disclose isolation of a gene encoding bovine protein disulfide isomerase that shows 60.7% sequence identity to the protein disulfide isomerase encoded by SEQ ID NO: 1. Furthermore Toyoshima et al. disclose expression of

human PDI using a vector (pT3BP-3) that encodes a polypeptide with protein disulfide isomerase activity showing 60.2% sequence identity to the protein encoded by SEQ ID NO: 1. Therefor these references clearly anticipate the protein disulfide isomerases broadly claiming any protein disulfide isomerases having at least 57% identity to the protein disulfide isomerases of SEQ ID NO: 2, and fragments of the same.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kagnew H Gebreyesus whose telephone number is 571-272-2937. The examiner can normally be reached on 8:30 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Achutamurthy ponnathapura can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kagnew Gebreyesus PhD.

Primary Examiner: Rao Manjunath PhD.
As Unit 1652.